

University of Groningen

Randomized controlled observer-blinded treatment of chronic foot eczema with iontophoresis and bath-PUVA

Tupker, Ron A; Coenraads, Pieter Jan; Zanen, Pieter; Schuttelaar, Marielouise

Published in:
Acta dermato-venereologica

DOI:
[10.2340/00015555-1537](https://doi.org/10.2340/00015555-1537)

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2013

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

Tupker, R. A., Coenraads, P. J., Zanen, P., & Schuttelaar, M. (2013). Randomized controlled observer-blinded treatment of chronic foot eczema with iontophoresis and bath-PUVA. *Acta dermato-venereologica*, 93(4), 456-460. <https://doi.org/10.2340/00015555-1537>

Copyright

Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

The publication may also be distributed here under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license. More information can be found on the University of Groningen website: <https://www.rug.nl/library/open-access/self-archiving-pure/taverne-amendment>.

Take-down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): <http://www.rug.nl/research/portal>. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.

CLINICAL REPORT

Randomized Controlled Observer-blinded Treatment of Chronic Foot Eczema with Iontophoresis and Bath-PUVA

Ron A. TUPKER¹, Pieter J. COENRAADS², Pieter ZANEN³ and Marie Louise A. SCHUTTELAAR²

Departments of ¹Dermatology and ³Research and Education, St. Antonius Hospital, Nieuwegein, and ²Department of Dermatology, University Medical Center Groningen, University of Groningen, The Netherlands

The aim of this study was to investigate the effect of iontophoresis combined with local psoralen plus ultraviolet A (PUVA) therapy in chronic foot eczema. A randomized, observer-blinded, multi-centre study was conducted in 48 patients with chronic moderate-to-severe foot eczema randomized to one of 3 groups: In the iontophoresis group local bath-PUVA was preceded by iontophoresis. In the PUVA group only local PUVA was given. The corticosteroid group was treated with fluticasone. All treatments were given for 8 weeks, with an 8-week follow-up period. The primary efficacy parameter was eczema score described by Rosén et al. Secondary efficacy parameters were a global impression by the patient, and the Dermatology Life Quality Index (DLQI). The eczema score and the DLQI decreased significantly over time. There were no significant differences in the decrease in eczema score ($p=0.053$) and DLQI values ($p=0.563$) between the 3 treatments. The DLQI values in our chronic foot eczema patients were high. There was no obvious advantage of local bath-PUVA with or without iontophoresis over local steroid therapy. **Key words:** PUVA therapy; iontophoresis; eczema; foot dermatoses.

Accepted Oct 3, 2012; Epub ahead of print Feb 18, 2013

Acta Derm Venereol 2013; 93: 456–460.

Marie Louise A. Schuttelaar, Department of Dermatology, University Medical Center Groningen, University of Groningen, PO Box 30.001, NL-9700 RB Groningen, The Netherlands. E-mail: m.l.a.schuttelaar@umcg.nl

Data on foot eczema (FE) are scarce and are often described in connection with hand eczema (1–4). Like hand eczema, FE can be classified according to aetiology and clinical features. Morphological types of hand eczema are vesicular (pompholyx type), hyperkeratotic/rhagadiform/tylotic, discoid (nummular patches) and combinations of these types (5). This classification probably also applies to FE.

Chronic eczema of the hands and feet is often refractory to conventional topical treatment such as corticosteroids, calcineurin inhibitors and coal-tar derivatives. Long-term systemic treatments (azathioprine, methotrexate, cyclosporine, retinoids and oral corticosteroids) are limited by their side-effects.

When a contact allergen is known or suspected, avoidance is the obvious choice, but does not always result in remission in FE. This may be explained by the occlusive effect of shoes and sweating. Hyperhidrosis is an aggravating factor in patients with palmoplantar pompholyx (3). Circumstantial evidence for the role of sweating in vesicular forms of hand eczema comes from studies demonstrating the efficacy of methods directed against hyperhidrosis. Tap-water iontophoresis was reported to be effective in an open study (6). In a subsequent study, botulinum toxin injections in the hands elicited good results in the majority of patients (7).

Another important treatment is photochemotherapy with psoralen plus ultraviolet A (PUVA). Local PUVA treatment has been used in uncontrolled studies in palmoplantar conditions with varying success rates (1, 2, 4). Better results were observed in vesicular types of eczema compared with hyperkeratotic types (1, 2, 4).

Since iontophoresis and local bath-PUVA are modalities with different mechanisms of action, the combination of these treatments was used successfully in 4 patients with chronic FE (8). The aim of the current study was to investigate further the effect of iontophoresis combined with local PUVA therapy on dermatitis activity in patients with chronic moderate to severe FE, who were responding insufficiently to topical therapy. This treatment was compared with local PUVA therapy only and topical corticosteroid therapy in a randomized observer-blinded trial.

MATERIALS AND METHODS

Trial design

Three treatments were investigated in parallel: (i) iontophoresis combined with local bath-PUVA therapy (“ionto+PUVA”); (ii) local bath-PUVA therapy only (“PUVA”); and (iii) topical corticosteroid therapy (“steroid”). The study was performed at 2 centres: University Medical Center Groningen and St Antonius Hospital, Nieuwegein. The study was observer-blinded.

Patients

Patients were eligible when ≥ 17 years old and diagnosed with at least 3 months’ duration of moderate-to-severe FE and an insufficient response to topical steroids, calcineurin inhibitors or coal-tar. Severity was defined according to the hand eczema score, as described by Rosén et al. (9). The following character-

ristics were evaluated: desquamation, erythema, vesiculation, infiltration, fissures and the patient's view on itch and pain. Each variable was assessed on a 4-point scale: none (0), slight (1), moderate (2) and severe (3). The maximum combined severity score was thus 21. Patients were included when this summed score was ≥ 8 .

Enrolment was open to patients with endogenous eczema and atopic dermatitis (AD). For AD the definition by the UK Working Party's diagnostic criteria was used (10). All patients were patch-tested. Patients were excluded if they had contact allergy, which was considered relevant for the eczema (=patients indicated an exacerbation of dermatitis after exposure to the allergen). Psoriasis and fungal infections were ruled out. Patients with concomitant hand eczema were included, but dermatitis on other body sites led to exclusion. In addition, all patients were tested for type 1 allergy (by prick testing and/or specific IgE antibodies).

Further exclusion criteria were: systemic therapy (antihistamines excluded) for eczema within 3 months before study entry, (local) UV therapy within 3 months before study entry, history of abnormal UV sensitivity, phototoxic or cytotoxic drugs, history of (pre)malignant skin conditions, metal-containing device (cardiac pacemaker, orthopaedic implants, gynaecological devices), pregnancy, large erosions which could not be protected sufficiently by petrolatum, decreased skin sensitivity (polyneuropathy), or history of low compliance with therapy.

At inclusion the following characteristics were evaluated: duration of eczema, results of patch testing for contact allergy, Fitzpatrick skin type, presence of plantar hyperhidrosis (patient's own view), smoking (if present, the number of pack years) and morphological type of eczema (vesicular or hyperkeratotic).

Patients were enrolled from July 2006 until January 2011. The study was performed in accordance with the Declaration of Helsinki and all applicable amendments. All patients gave written informed consent before enrolment and the study was approved by the ethics committee at each centre.

Randomization and treatment

Eligible patients were randomized to treatment via computer-generated random-number tables at each centre.

Tap-water iontophoresis. Tap-water iontophoresis was given 3 times weekly for 10 min using Hidrex® (GS Hidrex GmbH, Wuppertal, Germany). The direct current level was slowly increased, guided by the occurrence of tingling sensations. The maximum level was 30 mA. Iontophoresis was immediately followed by bath-PUVA.

Bath-PUVA. The psoralen bath was prepared by adding 8 ml 0.075 g/ml alcoholic stock solution of trimethylpsoralen to 3 l tap water to obtain a final trimethylpsoralen concentration of 0.2 mg/l. The soles were exposed to UVA radiation after soaking for 15 min. The initial UVA dose was 0.2 J/cm² in patients with skin type I/II, and 0.3 J/cm² in those with skin types III–VI. Dose increments were 0.2 J/cm² in patients with skin type I/II, and 0.3 J/cm² in those with skin types III–VI. The dose was not increased for one week in case of a slight erythema, followed by lower increments (0.1 J/cm² for skin types I/II, and 0.2 J/cm² for skin types III–VI). No treatment was given for one week in case of burning, followed by continuation with 70% of the last dose, and lower increments.

Irradiation was performed with Waldmann PUVA 180 L (Waldmann, Schwenningen, Germany) equipped with Sylvania F15W/T8. The irradiance at the surface of the patient's skin was, on average, 16 mW/cm² (Nieuwegein) and 16.4 mW/cm² (Groningen).

Steroid treatment. This consisted of fluticasone propionate 0.05% cream or ointment (GlaxoSmithKline, London, UK) applied initially 2 times daily. This was tapered-off by the

patients when the dermatitis showed a marked improvement on "GIP" (see below).

All patients used emollient ointments *ad libitum*, and antihistamines when necessary. All treatments were given for 8 weeks, followed by an 8-week follow-up period without topical steroid.

Efficacy assessments

The primary efficacy parameter was an eczema score derived from the hand eczema severity score as described by Rosén et al. (9) at 0, 4, 8, 12 and 16 weeks. Blinded evaluation was performed by a dermatologist (Nieuwegein) or a nurse practitioner experienced in eczema scoring (Groningen). Secondary efficacy parameters were global impression by the patient (GIP) and the patient's view on plantar hidrosis by means of a 4-point scale ("0", no improvement or worse; "1", moderate improvement; "2", marked improvement; "3", cleared). Furthermore, the patient's quality of life was evaluated by means of Dermatology Life Quality Index (DLQI), according to Finlay & Khan (11), at 0, 8 and 16 weeks. The DLQI is a composite index with a total score that ranges from 0 (best quality of life) to 30 (poorest quality of life).

Statistical analysis

Normally distributed data are listed as mean (standard deviation (SD)), non-normally distributed continuous data as median (q25, q75), nominal/ordinal data via frequencies and cross-tables.

Baseline characteristics were evaluated via analysis of variance, including treatment and centre as factors for normally distributed data or via Kruskal–Wallis test for non-normally distributed data.

This study describes time-dependent observations, which are correlated by definition. The appropriate analytical approach in such cases is the random intercept, random coefficient linear mixed model (12). Parameters, such as the eczema score and DLQI, are regressed on time (=weeks of treatment) and time is considered to be the random factor. Other relevant factors, such as "treatment group", "centre" were introduced into the analysis as independent fixed factors, and their interaction with time. The latter informs on whether the differences between treatments and centres are constant over time.

Global impression by the patient and the patient's view on plantar hidrosis are ordinal 4-point scale parameters. For these variables the generalized estimation equations analyse for time-dependent ordinal parameters were used.

SPSS 19 was used and *p*-values <0.05 were considered significant. Evaluation is according to the intention-to-treat principle.

RESULTS

A total of 48 patients entered the study. Nineteen patients were allocated to iontophoresis with local PUVA therapy ("ionto+PUVA"), 14 to local PUVA therapy alone ("PUVA"), and 15 to topical fluticasone ("steroid"). Of these, 5 patients in the ionto+PUVA group, 6 patients in the PUVA group and 2 patients in the steroid group did not complete the trial (Fig. 1). Taken together, 27% of the patients discontinued after allocation.

The 3 treatment groups did not differ in any of the baseline characteristics (Table I). The discontinued patients groups did not differ in any of the baseline characteristics (data not shown).

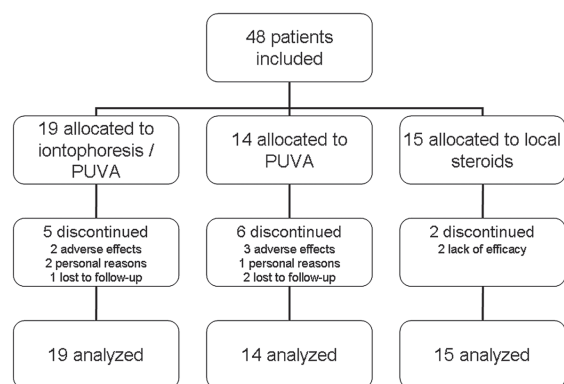


Fig. 1. Participant flow through the trial. PUVA: psoralen plus ultraviolet A.

Two patients in the ionto+PUVA group and 3 patients in the PUVA group experienced burning during therapy. Burning in combination with the lack of efficacy was, for these patients, the main reason to withdraw from the study. One patient in each group had mild erythema. These side-effects disappeared after adjusting the UVA dose.

The mean cumulative values for UVA dose (\pm SD) in the ionto+PUVA group and PUVA group were 27.3 and 31.2 J/cm², respectively. The mean cumulative value for iontophoresis dose in the into+PUVA group was 245 mA.

The time-dependent decrease in eczema score, broken down by treatment group, is shown in Fig. 2. The decrease in the eczema score over time (irrespective of the type of treatment) was highly significant ($p < 0.001$), from an initial 10.69 to 6.87 points at end-observation. The differences between the 3 treatments on the eczema score was not significant ($p = 0.053$), and the treatment*time interaction ($p = 0.075$) was also not significant. The latter indicates that the decrease in the eczema score over time was not different between the 3 treatment groups. The centre*time interaction was not

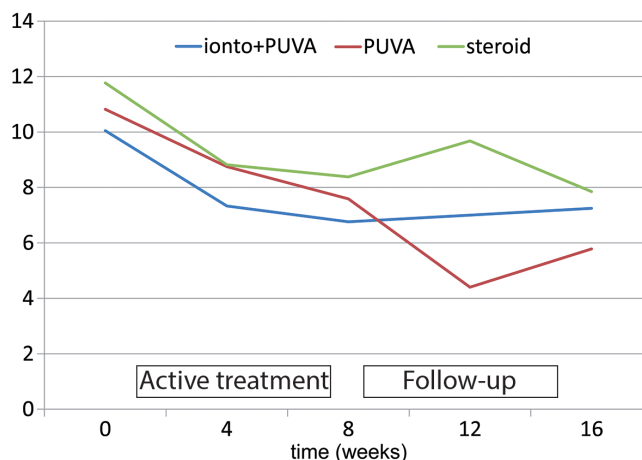


Fig. 2. Eczema score over time. PUVA: psoralen plus ultraviolet A; ionto: iontophoresis.

significant ($p = 0.778$): the eczema score decreased by similar levels over time at both centres.

Neither the type of eczema (vesicular vs. hyperkeratotic) ($p = 0.498$) nor the presence of hidrosis ($p = 0.127$) predicted the decrease of the eczema score over time. The same was true for the variables age, sex, duration of eczema and smoking (data not given).

The time-dependent decrease in DLQI score broken down by the treatment group is shown in Fig. 3. The decrease in the DLQI score over time was highly significant ($p < 0.001$), from an initial 12.23 to 7.78 points at end-observation. However, neither the difference between the 3 treatments on the DLQI score was significant ($p = 0.563$), nor was the treatment*time interaction ($p = 0.564$). The type of eczema (vesicular vs. hyperkeratotic) ($p = 0.042$) was a weak significant predictor of the overall DLQI score. Hyperkeratotic eczema elicited a 3.15 higher DLQI score (95% CI 0.12–6.187). The eczema type*time and the eczema type*centre interactions were both non-significant ($p = 0.554$ and $p = 0.937$, respectively). Therefore, the eczema type had no influence on the effect of treatments. The presence of hyperhidrosis

Table I. Characteristics of the patients at baseline

	ionto+PUVA (n = 19)	PUVA (n = 14)	Steroid (n = 15)
Age, years, mean (SD)	37.9 (11.5)	38.6 (11.1)	41.6 (11.6)
Males/females, n	8/11	10/4	6/9
Endogenous/atopic, n	12/6	11/3	13/2
Duration of eczema, years, mean (SD)	4.6 (4.6)	4.9 (4.4)	6.4 (10.1)
Rosén score, mean (SD)	10.1 (2.1)	10.8 (2.4)	11.8 (3.4)
Dermatology Life Quality Index, mean (SD)	13.4 (5.7)	11.2 (4.3)	11.8 (6.0)
Plantar hyperhidrosis yes/no, n	8/11	10/4	8/7
Smoking yes/no, n	11/8	11/3	11/4
Morphological type, n			
Vesicular	14	4	11
Hyperkeratotic	5	10	4
Centre, n			
Groningen	9	11	9
Nieuwegein	10	3	6

SD: standard deviation; ionto: iontophoresis; PUVA: psoralen plus ultraviolet A.

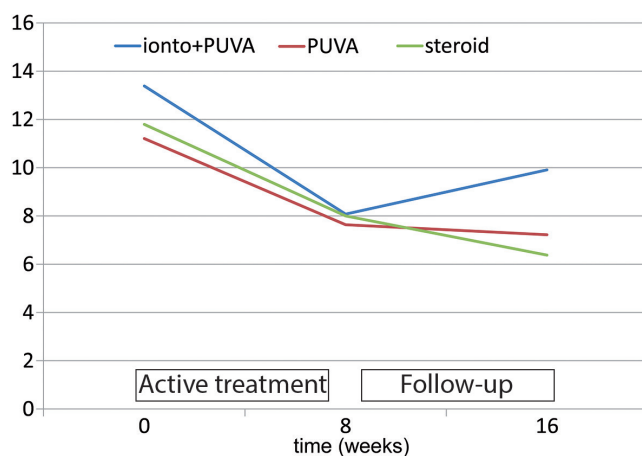


Fig. 3. Dermatology Life Quality Index (DLQI) over time. PUVA: psoralen plus ultraviolet A; ionto: iontophoresis.

was a non-significant ($p=0.078$) predictor of the DLQI score decrease over time. When DLQI over time is the dependent variable no influence was noted of treatment, time, centre, type of eczema and hyperhidrosis.

The decrease in the GIP score over time was non-significant ($p=0.828$), from an initial median 1 to 0 points at end-observation.

The degree of hidrosis as judged by the patients decreased over time only in the onto+PUVA group ($p=0.143$ for differences between groups).

DISCUSSION

This study investigated the efficacy of iontophoresis combined with local bath-PUVA, and the efficacy was compared with that of topical steroids and local bath-PUVA only. There were no significant differences between these 3 treatments for the decrease in the eczema score and DLQI values. DLQI values in these chronic FE patients were high, particularly for hyperkeratotic eczema. Eczema type or hyperhidrosis had no influence on the effects of treatments with respect to the eczema score and DLQI.

An eczema severity score was chosen as the primary efficacy parameter for dermatitis severity (9). This composite instrument measures several objective and 2 subjective characteristics of hand eczema. It is not validated for FE, but no validated instruments to assess FE severity are available. DLQI is a well-known measure for estimating quality of life, validated for various dermatological conditions (11) but not specifically for FE.

Local bath-PUVA is a widely accepted and effective second-line modality in the treatment of hand and foot eczema (13). Therefore, we decided not to include a placebo arm in this study on ethical grounds. The high disease burden and the well-known effects of the reference therapies eliminate the need for a placebo-controlled study.

The high drop-out rate of 27% may be considered a potential source of bias, as most of the drop-outs were due to non-efficacy or side-effects not outweighing efficacy. Such subjects may negatively influence the overall efficacy estimates of the 3 therapies. Excluding these subjects from the analysis would falsely augment therapeutic efficacy estimates. Fortunately, the statistical method used to evaluate the data is not sensitive to premature drop-out. Per subject the decline over time of the parameters is estimated and a minimum of 2 data-points is needed for that. So a late drop-out (after 2 data-points), due to, for example, non-efficacy, provides an estimate of decline and, when this is low or negative, the overall group efficacy is influenced by this. Once again, the discontinued patients did not differ in any of the baseline characteristics.

The decrease in the eczema score in our study was approximately 4 points (over the 3 treatments) and we

consider this decrease as clinically highly relevant. In previous studies on FE, local PUVA induced complete remission or marked improvement in 80–89% of the patients (1, 2). However, these studies had an open design and were not blinded (1, 2). Furthermore, dermatitis severity at baseline was also not stated, and the therapeutic response was graded only qualitatively. In a more recent investigation local PUVA was compared with oral PUVA in a randomized observer-blinded manner (4). The treatment effects were scored with a modified Psoriasis Area and Severity Index (PASI) system, and that score decreased from 11.5 to 3.7 for local PUVA, with a similar decrease for oral PUVA ($p=0.67$ for the difference between treatments) (4). In a study on vesicular hand eczema topical PUVA was compared with UVA without psoralen in a right–left patient-blinded way (14). Both PUVA and UVA treatments resulted in a significant decrease from 27 to 9 on a semi-quantitative scoring scale after 8 weeks therapy, without a difference between the 2 treatments (no p -values reported).

In previous studies better results were observed for vesicular, as opposed to hyperkeratotic, eczema types (1, 2, 4). In hyperkeratotic eczema bath-PUVA resulted in a moderate improvement, whereas oral PUVA had a significantly better response, presumably because of impaired penetration of 8-methoxypsoralen through the thickened epidermis (4).

In a small open observational study on the combination of iontophoresis with local PUVA (8) clearance or marked improvement was observed in 4 out of 5 treatments, but the current better designed investigation could not confirm the alleged superiority of the combination therapy. In another (right–left) study on vesicular hand eczema, iontophoresis had a favourable effect on vesicles and pruritus scores, but not on erythema and scaling scores (6). In that study the same iontophoresis device was used as in our study, and was given daily for 3 weeks. No mention was made of the cumulative mA values or of the presence of hyperhidrosis (6). It is difficult to compare the outcome of that study with that of our study because of lack of details.

Comparison of the results of the above-mentioned studies is hampered by the fact that different scoring systems were used in small unbalanced groups, evaluated by statistical methods that did not meet the appropriate standards. In contrast, our results are based on the best available scoring systems and are analysed by appropriate statistics, which were interpreted strictly. These powerful analyses point towards the notion that there is no additional advantage of local PUVA with or without iontophoresis over local steroid therapy.

The DLQI score showed a significant decrease over time, with no differences between the treatment groups. There was no influence of eczema type on this decrease, although the hyperkeratotic type was generally associated with lower quality of life than the vesicular

type. The overall DLQI score at baseline was 12.2. To our knowledge, there are no data on quality of life for FE, in contrast to those for hand eczema. For hand eczema reported DLQI scores were 9.7 (15) and 8.0 (16). In their original description Finlay & Khan (11) measured the DLQI in a variety of skin diseases and healthy controls. The highest value was 12.5, found in AD patients. The high DLQI values in our study may be due to a more severe dermatitis. Thus, apparently in our groups FE is characterized with a high disease burden, comparable with that in AD, but higher than that in hand eczema. This high DLQI found in our FE patients is remarkable in view of the fact that the feet are supposedly not involved in the DLQI items leisure and personal relationships to the same extent as in AD and hand eczema. Our study showed higher DLQI values in hyperkeratotic eczema vs. vesicular eczema. For hand eczema no DLQI differences between vesicular and hyperkeratotic forms were observed (16). It is unclear whether this discrepancy is due to the unique character of FE as opposed to hand eczema. DLQI may influence patient-rated severity score and may be responsible for the discrepancy between the patient-rated and physician-rated scores in hand eczema (15). Our findings on FE must await further confirmation in future studies.

A significant benefit of combined iontophoresis–bath-PUVA in comparison with bath-PUVA only and topical steroid therapy could not be demonstrated in this study. All treatments induced improvement. These results may be because of the study design using a comparison between 3 active treatments. Introducing a placebo group is unethical given the high disease burden in our patients. Moreover, it makes more sense to compare the efficacy of the novel therapy with a first-line treatment (in this case topical steroids) (17). To the best of our knowledge, there are only 2 comparative studies on palmoplantar eczema without a placebo group (4, 14). In those studies too, no differences were observed between the treatment groups, which consisted of UVA therapy only. Our study has demonstrated that in each treatment group there were responders and non-responders. This is probably caused by the fact that patients behave differently by genetic mechanisms and also by the fact that they may become resistant to previously given therapies.

In dermatological practice topical steroid treatment is regarded as a first choice. Therefore, local bath-PUVA may be offered when patients are resistant to local steroids.

ACKNOWLEDGEMENTS

We thank J. L. van Velde, Dermatologist, St Antonius Hospital, Nieuwegein and N. Drukker, Nurse Practitioner, University Medical Center Groningen, for their help in assessing the ef-

ficacy parameters. We also thank M. J. van Es, MD, Groningen, for assistance in recruiting the patients and data entry.

The authors declare no conflicts of interest

REFERENCES

1. Schempp CM, Müller H, Czech W, Schöpf E, Simon JC. Treatment of chronic palmoplantar eczema with local bath-PUVA therapy. *J Am Acad Dermatol* 1997; 36: 733–737.
2. Behrens S, von Kobyletzki G, Gruss C, Reuther T, Altmeyer P, Kerscher M. PUVA-bath photochemotherapy (PUVA-soak therapy) of recalcitrant dermatoses of the palms and soles. *Photodermatol Photoimmunol Photomed* 1999; 15: 47–51.
3. Guillet MH, Wierzbicka E, Guillet S, Dagregorio G, Guillet G. A 3-year causative study of pompholyx in 120 patients. *Arch Dermatol* 2007; 143: 1504–1508.
4. Tzaneva S, Kittler H, Thallinger C, Hönigsmann H, Tanew A. Oral vs. bath PUVA using 8-methoxypsoralen for chronic palmoplantar eczema. *Photodermatol Photoimmunol Photomed* 2009; 25: 101–105.
5. Diepgen TL, Anderssen KE, Brandao FM, Bruze M, Bruynzeel DP, Frosch P, et al. Hand eczema classification: a cross-sectional, multicentre study of the aetiology and morphology of hand eczema. *Br J Dermatol* 2009; 160: 353–358.
6. Odia S, Vocks E, Rakosi J, Ring J. Successful treatment of dyshidrotic hand eczema using tap water iontophoresis with pulsed direct current. *Acta Derm Venereol* 1996; 76: 472–474.
7. Swartling C, Naver H, Lindberg M, Anvelden I. Treatment of dyshidrotic hand dermatitis with intradermal botulinum toxin. *J Am Acad Dermatol* 2002; 47: 667–671.
8. Tupker RA. Successful treatment of severe foot dermatitis by iontophoresis and local bath-PUVA. *Acta Derm Venereol* 2004; 84: 70–71.
9. Rosén K, Mobacken H, Swanbeck G. Chronic eczematous dermatitis of the hands: a comparison of PUVA and UVB treatment. *Acta Derm Venereol* 1987; 67: 48–54.
10. Williams HC, Burney PGJ, Pembroke AC, Hay RJ. The U.K. Working Party's diagnostic criteria for atopic dermatitis. III. Independent hospital validation. *Br J Dermatol* 1994; 131: 406–416.
11. Finlay AY, Khan GK. Dermatology Life Quality Index (DLQI): a simple practical measure for routine clinical use. *Clin Exp Dermatol* 1994; 19: 210–216.
12. Hedeker D, Gibbons RD. Longitudinal data analysis. New Jersey: John Wiley & Sons, Inc., 2006.
13. Pryzbilla B, Ruëff F. Contact dermatitis. In: Burgdorf WHC, Plewig G, Wolff HH, Landthaler M, editors. *Braun-Falco's dermatology*. 3rd edn. Heidelberg: Springer-Verlag, 2009: p. 377–401.
14. Grattan CEH, Carmichael AJ, Shuttleworth GJ, Foulds IS. Comparison of topical PUVA with UVA for chronic vesicular hand eczema. *Acta Derm Venereol* 1991; 71: 118–122.
15. van Coevorden AM, van Sonderen E, Bouma J, Coenraads PJ. Assessment of severity of hand eczema: discrepancies between patient- and physician-rated scores. *Br J Dermatol* 2006; 155: 1217–1222.
16. Agner T, Andersen KE, Brandao FM, Bruynzeel DP, Bruze M, Frosch P, et al. Hand eczema severity and quality of life: a cross-sectional, multicentre study of hand eczema patients. *Contact Dermatitis* 2008; 59: 43–47.
17. Rothman KJ. Placebo mania. *Br Med J* 1996; 313: 3–4.